Medical and Pediatric Oncology 28:98–107 (1997)

Intermediate-Dose Methotrexate Versus Cranial Irradiation in Childhood Acute Lymphoblastic Leukemia: A Ten-Year Follow-Up

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The cure rate of childhood acute lymphoblastic leukemia (ALL) has improved dramatically. Still there is a paucity of long-term data. With the improving cure rate, the quality of life and avoidance of second cancers have become important concerns.

We evaluated 596 children and adolescents with ALL on Cancer and Leukemia Group B 7611 (CALGB 7611) who were randomized between 1976 and 1979 to receive intermediate-dose methotrexate (IDM) plus intrathecal methotrexate (IT MTX) or cranial radiation (CRT) plus IT MTX.

After 10 additional years of follow-up, the pattern and significance of the results reported in 1983 are confirmed. IDM offered better hematologic protection ($P < 0.0006$), better testicular protection ($P = 0.002$), but CRT offered better central nervous system (CNS) protection ($P < 0.0001$). The retrieval rate for the 231 patients who relapsed while on therapy or within 6 months of elective cessation of therapy is 20 ± 5%. For the 33 patients who relapsed more-than 6 months after cessation of therapy, the retrieval rate is 49 ± 10%. For all patients, the 12-year event-free survival was 37 ± 3.6% and the overall survival was 49 ± 3.5%. There were two cases of second malignancies reported in 3,502 person-years of survival. Both occurred following salvage therapy. There was no evidence of an excessive number of second primaries over the general population of children. There were no reported instances of clinical cardiopathy.

After a median follow-up of 11 years, there have been no reports of cardiopathy and no evidence of an increased risk of second cancers in children treated on CALGB 7611. While the overall outcome is not what would be expected with modern therapy, one can conclude that CRT offered better CNS protection, but IDM offered better systemic and testicular protection. A small risk of second cancers or cardiac dysfunction may be acceptable with therapies which produce long-term documented survival benefits. **Med. Pediatr. Oncol. 28:98–107**

Key words: childhood ALL; intermediate-dose methotrexate; cranial irradiation; long-term follow-up

INTRODUCTION

In 1983 Cancer and Leukemia Group B (CALGB) published the results of intermediate-dose methotrexate (IDM) given intravenously at 500 mg/m^2 three times compared with cranial irradiation of 2,400 cGy in children with acute lymphoblastic leukemia (ALL) (CALGB 7611) [1]. Both arms also received intrathecal methotrexate (IT MTX) and all the patients received continuation therapy with a standard maintenance regimen of daily 6 mercaptopurine (6-MP) and weekly oral methotrexate with periodic pulses of intravenous vincristine and oral prednisone. This trial was designed to evaluate whether IDM could substitute for cranial radiation (CRT) since data were already emerging that CRT could adversely affect intelligence. Furthermore, IDM had the theoretical advantage of potentially affecting leukemic rests in regions other than the central nervous system (CNS), such as the gonads, liver, spleen, and marrow. This was one of the first major randomized multicenter studies evaluating the omission of CRT in ALL. It was one of the first studies attempting to test both early and late intensification of chemotherapy dosing in ALL in a randomized trial.

In brief, the results published in 1983, based upon a

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Received 22 November 1995; accepted 4 March 1996.

1981 analysis at a median observation time of 40 months, showed that IDM offered better systemic protection against relapse in standard-risk patients and better protection against testicular relapse in all patients, but CRT offered superior CNS protection. The overall disease-free survival and survival in both treatment groups were nearly identical.

In 1991 CALGB 7611 was reevaluated to determine how the findings had matured over the intervening 10 years. In addition, the salvage rates for those patients relapsing both on and off therapy were evaluated, as was the incidence of second primary cancers. This was thought to be of importance since, with the exception of CRT, known carcinogenic agents such as alkylating agents and epipodophylltoxins were not employed in this study [2]. Evaluations were screened for cases of reported clinical cardiopathy.

The CALGB 7611 enrolled patients from November 12, 1976 until July 16, 1979 when the study was closed. All patients as of 1991 had completed their prescribed 3 years of first-line therapy at least 9 years previously. This is relevant since most, if not all, failures would have occurred by 1991.

MATERIALS AND METHODS

Methods were previously described in detail [1]. Briefly, untreated children and adolescents less than 20 years of age with ALL, including undifferentiated leukemia, were eligible for the study. Since the study was opened in 1976 cell surface markers and cytogenetics were not mandated nor was the French-American-British classification used. Remission was determined by bone marrow aspirates on days 28 and 42 and every 3 months during treatment thereafter, or when relapse was suspected. Remission was indicated by bone marrow with normal granulopoiesis, thrombopoiesis, and erythropoiesis with less than 5% lymphoblasts and less than 40% total lymphocytes and lymphoblasts. For purposes of analysis, failure was defined as: 1) termination of complete remission due to bone marrow relapse (more than 25% blasts); 2) central nervous relapse (definite blast cells on cytologic preparations [cytospin] or 10 mononuclear cells per microliter whose presence was not attributed to chemical meningitis); 3) biopsy-confirmed leukemic relapse in an extramedullary organ; or 4) death during complete remission. If a patient had experienced a relapse of any type, the treatment was considered to have failed.

We analyzed the fate of patients who relapsed while on therapy or within 6 months after its completion. We also analyzed the fate of patients who relapsed 6 months or more after cessation of planned chemotherapy. These patients have all been tracked to death or for greater than 5 years following their first relapse. We did not capture the specific type of salvage therapy used. Salvage or retrieval was defined as induction into a second complete remission into disease-free survival persisting at the time of the 1991 analysis. Also, all surviving patients were surveyed for second primary neoplasms.

Statistics

The original study design required 150 patients who achieved remission to be randomized to receive IDM or CRT after being stratified according to CALGB risk criteria; a patient was considered to be at standard risk if the initial white cell count was less than 30,000 and if the age was more than 2 but less than 8 years. All other patients were classified as being at increased risk. This sample size was calculated to provide 80% power ($\alpha = 0.05$) to detect a 33% reduction in the relapse rate for the IDM arm as compared to the CRT arm. The study was subsequently amended to ensure that 300 patients in continuous complete remission (CCR) for 3 years would be available for randomization to end intensification or observation after stratifying by initial treatment assignment. This sample size was to have provided 95% power ($\alpha = 0.05$) to detect a 15% difference in the relapse rates of the observation and end intensification arms.

Kaplan-Meier [3] estimates of event-free survival (EFS), duration of CCR, and survival were compared using a stratified Mantel-Haenszel statistic [4]. Standard errors (SE) of these estimates have been calculated using the technique proposed by Peto and coworkers [5] and appear in the text following the estimates as $\pm$SE. EFS and survival were measured from the date of initiation of induction therapy until failure. Duration of CCR was measured from the date of ramdomization until failure. Inferences regarding treatment and site-specific failure were based on methods described by Kalbfleisch and Prentice [6] and Gray [7]. These methods provide control for competing risk of failure. The cumulative incidence functions provide estimates for the probability that the first failure of a specified nature occurs by a given time. All other failures are censored. Cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER) data [8] of the National Cancer Institute were used to calculate the number of second cancers expected for the observed person-years of survival accumulated by the total study group. Person-years of survival was measured from initiation of induction therapy until the dates of death or last contact. Age, sex, and race-adjusted incidence rates for the years 1981–1985 were used. Comparison of the observed rate to that predicted by SEER data was made using confidence intervals for the ratio of a Poisson variable to its expected value [9]. Due to the small number of second cancers, no estimate of cumulative risk was calculated.

With the single exception of an institution discussed below, the effort to obtain follow-up information on patients about whom no data had been gathered in 8 years was a success. All follow-up information was obtained through physicians responsible for the patients. We em-

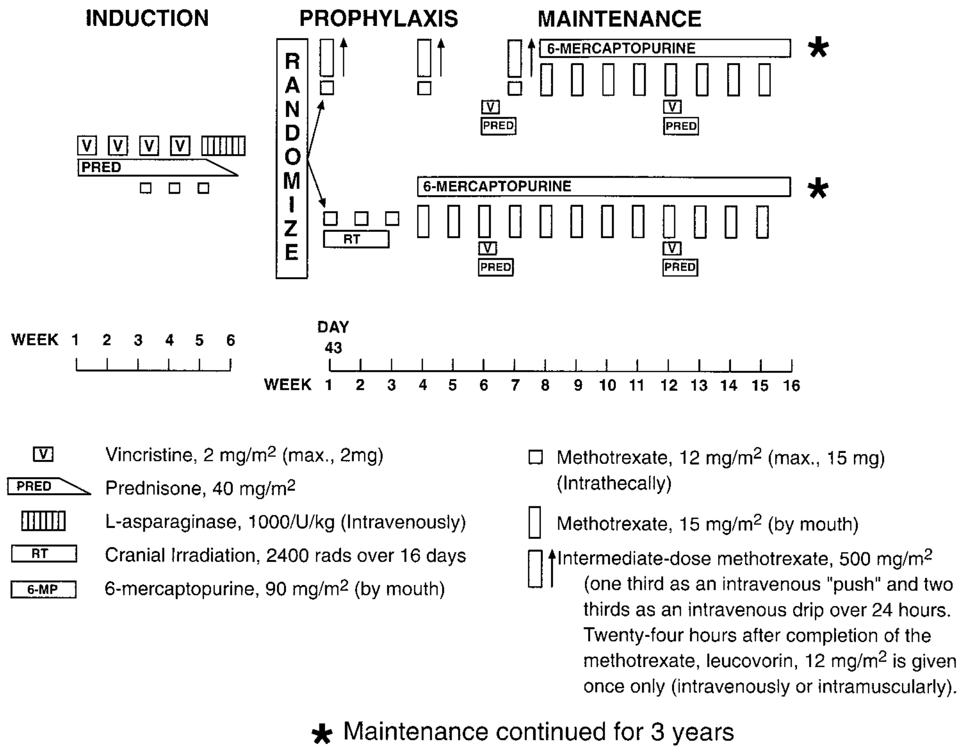

Fig. 1. Treatment phases of CALGB protocol 7611 (treatment of primary untreated acute lymphocytic leukemia in patients under 20 years).

ployed precoded data capture forms and confirmed that the medical records had been reviewed by collecting some data which already existed in the database. Of 358 children treated on CALGB 7611 who were known to have been alive in 1983, additional information was received on 266 (74.3%). Of the 278 patients who have never failed, the years of last contact are 1989–1991 for 170 (61.2%), 1985–1988 for 34 (12.2%), 1981–1984 for 46 (16.5%), and 1979–1980 for 28 (10%). Our efforts to obtain information ended in July 1991. One institution, at which 87 children had been randomized, failed to provide any follow-up information in 1983 and a decision was therefore made not to request follow-up information on the 53 children who were last recorded as being alive. These 87 patients nonetheless are included in all analyses using all information previously provided.

Treatment

The induction consisted of intravenous vincristine, 2 mg/m^2; four doses (maximum single dose of 2 mg) oral prednisone, 40 mg/m^2 per day given for 4 weeks and then tapered; IT MTX, 12 mg/m^2 for three doses (maximum dose of 15 mg); and intravenous asparaginase, 1,000 units/kg of body weight per day for 10 doses. The patient was randomized after complete remission and 10 days of asparaginase to IDM or CRT (Fig. 1).

Prophylactic (Intensified) Phase

IDM was administered over 24 hours at a dosage of 500 mg/m^2 per day on three occasions at 3-week intervals. A single dose of leucovorin (12 mg/m^2) was administered 24 hours after completion of IDM administration (i.e., 48 hours of methotrexate exposure). IT MTX was given ½ and 2 hours after the start of IDM on three occasions.

CRT was given over 16 days in 200 cGy increments for a total of 2,400 cGy. The radiation field included the entire brain and meningeal surfaces, the cribriform plate, and the posterior half of the orbit, including the optic discs. The anterior chamber of the eye, including the lens, was shielded. The patients were treated with two lateral parallel opposed fields. IT MTX, 12 mg/m^2 (maximum single dose, 15 mg) weekly for three doses, was also administered during the period of CRT.

Maintenance Phase

Upon completion of the prophylactic (early intensification) phase, all patients received the same maintenance therapy, consisting of oral mercaptopurine (90 mg/m^2 per day) plus oral methotrexate (15 mg/m^2 per week). Reinforcement courses of vincristine and prednisone were given at weeks 6, 12, 16, 20, and 24 after the start of prophylactic therapy; starting at week 28, two weekly doses of vincristine plus 2 weeks of prednisone treatment were given, without tapering of the doses, every 12 weeks for the duration of maintenance.

Late Intensification Phase

After 3 years of maintenance therapy, patients were completely reevaluated by bone marrow aspiration and a diagnostic lumbar puncture to determine their status with

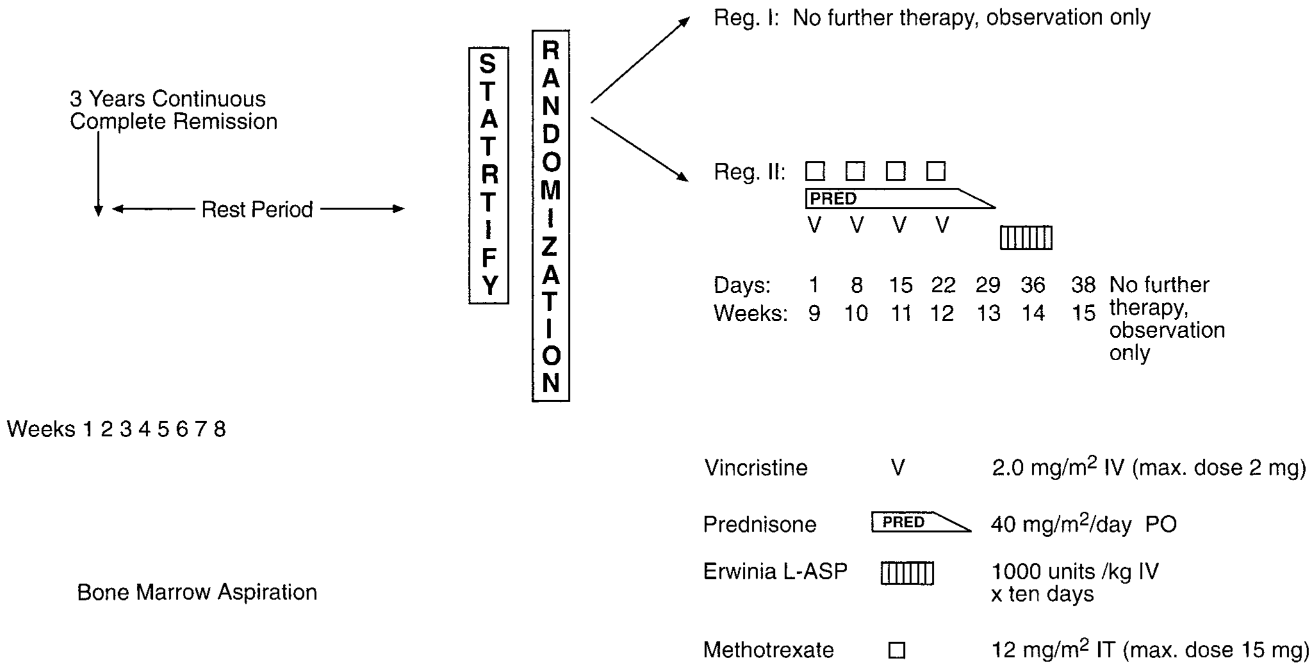

Fig. 2. CALGB 7611 comparing end intensification with observation in those patients who completed 3 years of CCR.

regard to remission. Patients in complete remission were then randomized to receive late intensification or not. Late intensification consisted of 4 weeks of prednisone at 40 mg/m^2 per day orally, vincristine at 2 mg/m^2 weekly times four injections (maximum dose 2 mg), and L-asparaginase 1,000 units per mg/m^2 daily for 10 days. In addition, three doses of IT MTX at 12 mg/m^2 (maximum 15 mg) were administered on three occasions. The intensification was similar to the initial induction and was utilized to test the Norton-Simon hypothesis [10] that late intensification improves outcome (Fig. 2).

RESULTS

The analysis reported in 1983 [1] covered all available data through April 1981 corresponding to a median follow-up of approximately 40 months. Subsequent data have resulted in minor changes in the number of children eligible for analysis. Furthermore, the original reasons for postrandomization exclusions [1] have been reevaluated resulting in additional patients for analysis. Between November 12, 1976 and July 16, 1979, 634 children were enrolled in CALGB 7611. Five-hundred ninety-six (94%) are eligible and evaluable for response to induction (compared to the 600 previously reported), survival, and EFS. Five-hundred forty-six (92%) achieved remission. Eleven of the responders were never randomized. Of the 535 children randomized, 10 (1.8%) could not be included in analyses of treatment-specific outcomes for the following reasons: they were lost before initiation of sanctuary treatment (six); refused randomized treatment—no data (two); and inadequate data (two). Thus, 525 children were evaluable (previously 506) and randomized to receive either IDM (266) or CRT (259). The current data have a median follow-up of patients who remain at risk for failure of approximately 8 years. (Excluding the early censored patients from the one problem institution, the median follow-up is 11 years.)

The conclusions remain the same as those reported in 1983. The distributions of duration of CCR are not significantly different ($P > 0.7$, Fig. 3). The CCR rates for IDM and CRT at 12 years are 40 ± 5.4% and 40 ± 5.9%, respectively. Protection against hematologic relapse as measured by cumulative incidence was superior for all children randomized to IDM ($P < 0.0006$, Fig. 4), and was most evident in the standard-risk patients. Protection against CNS relapse was superior for CRT ($P < 0.0001$, Fig. 5), and the differences were statistically significant in all risk groups. IDM had poor CNS protection and males were no more likely than females to experience an isolated CNS relapse ($P > 0.7$). The CRT offered reasonable CNS control and again there was no difference in CNS relapse rates between the sexes ($P > 0.2$). Males randomized to receive IDM have significantly improved protection against testicular relapse ($P = 0.002$, Fig. 6)

After 3 years of CCR, patients were evaluated with bone marrow and lumbar puncture and those in complete remission were to have been randomized to receive end intensification therapy or no further treatment. Unfortunately, at that time many patients, families, and investiga-

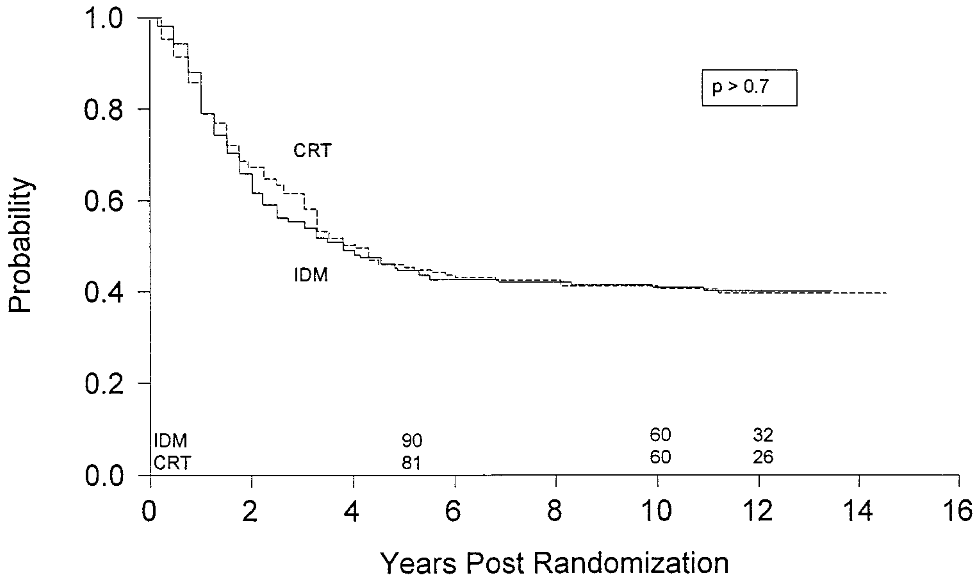

Fig. 3. Duration of CCR in the IDM (N = 266) and CRT (N = 259) arms. The numbers above the time axis are the numbers of patients who remain at risk for failure at 5, 10, and 12 years. The estimates of 12-year CCR rates for the IDM and CRT arms are 40 ± 5.4% and 40 ± 5.9%, respectively.

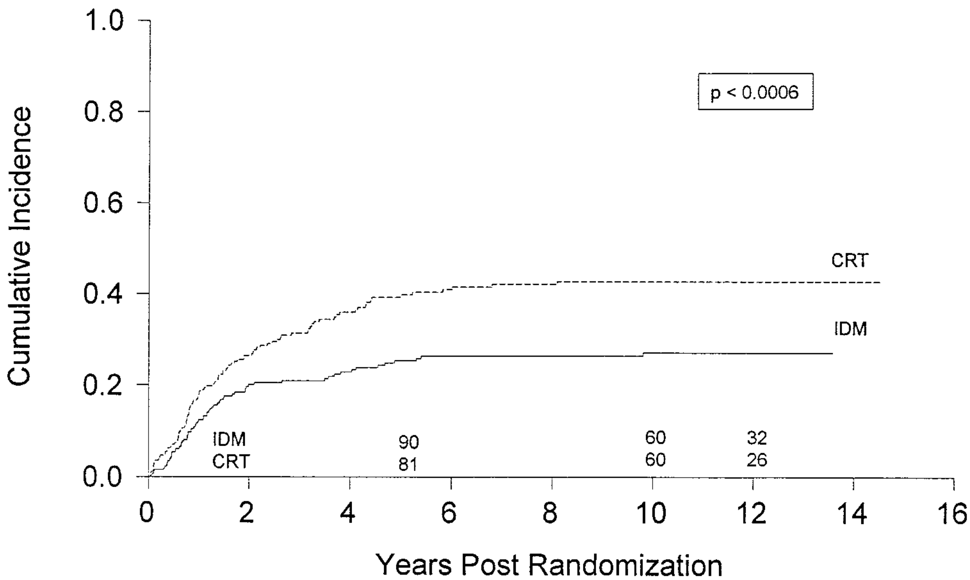

Fig. 4. Cumulative incidence functions of hematologic relapse as a first event in the IDM (N = 266) and CRT (N = 259) arms. The numbers above the time axis are the numbers of patients who remain at risk for failure at 5, 10, and 12 years. The estimates of 12-year incidence rates for the IDM and CRT arms are 27 ± 3% and 43 ± 3%, respectively.

tors were reluctant to participate in this phase of the clinical trial and too patients were actually randomized (observation: n = 49; end intensification: n = 40) for any meaningful comparison. The results are inconclusive ($P = 0.22$) that end intensification improved outcome, due to insignificant patient numbers and resultant low statistical power (data not shown).

For all patients initially randomized who completed 3 years of therapy on CALGB 7611 in CCR (n = 247), the estimate of probability of subsequent failure is 30 ± 5.0%. There is no evidence of a difference in distribution of CCR between CRT and IDM treatments ($P > 0.2$) for these patients.

Survival 10 years after relapse for the 231 patients who relapsed on or within 6 months of cessation of therapy is 20 ± 5%. No patient has died more than 5 years after initial relapse. For the 33 patients who relapsed more than 6 months after elective cessation of therapy, survival 5 years after relapse is 49 ± 10% and only one death was reported after 5 years. In either case, there is no evidence of a difference in survival between the IDM and CRT arms ($P > 0.6$ and $P > 0.6$, respectively).

Twelve-year EFS (Fig. 7) for the 596 eligible children evaluable for response was 37 ± 3.6% and 64 children have been followed for more than 12 years. No failure has been reported after 12 years of follow-up. Based on the 596 eligible children evaluable for response, the 12-year survival rate is 49 ± 3.5% (Fig. 7). The 12-year

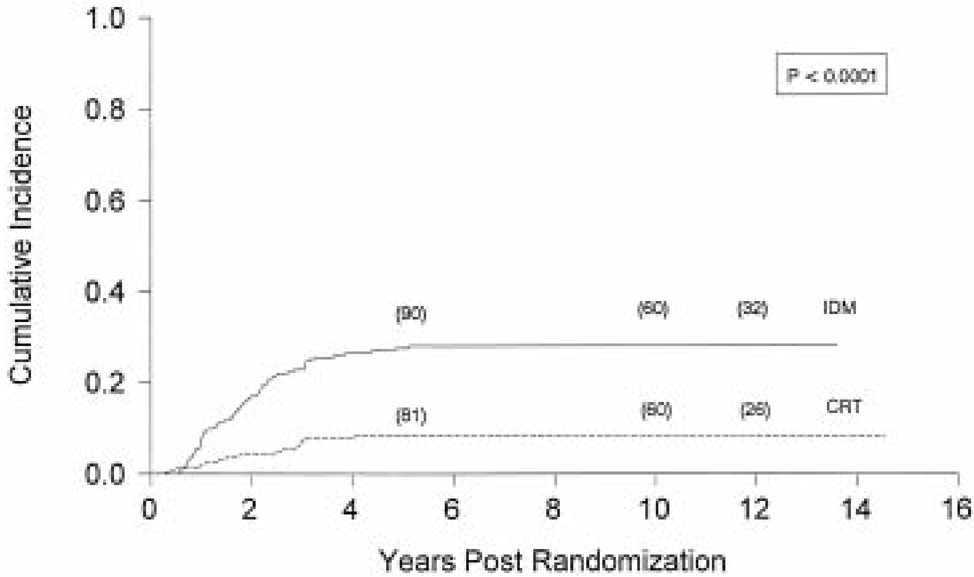

Fig. 5. Cumulative incidence functions of CNS relapse as a first event for the IDM (N = 266) and CRT (N = 259) arms. The numbers in parentheses above the plots are the numbers of patients who remain at risk for failure at 5, 10, and 12 years. The estimates of 12-year incidence rates for the IDM and CRT arms are 28 ± 3% and 8 ± 2%, respectively.

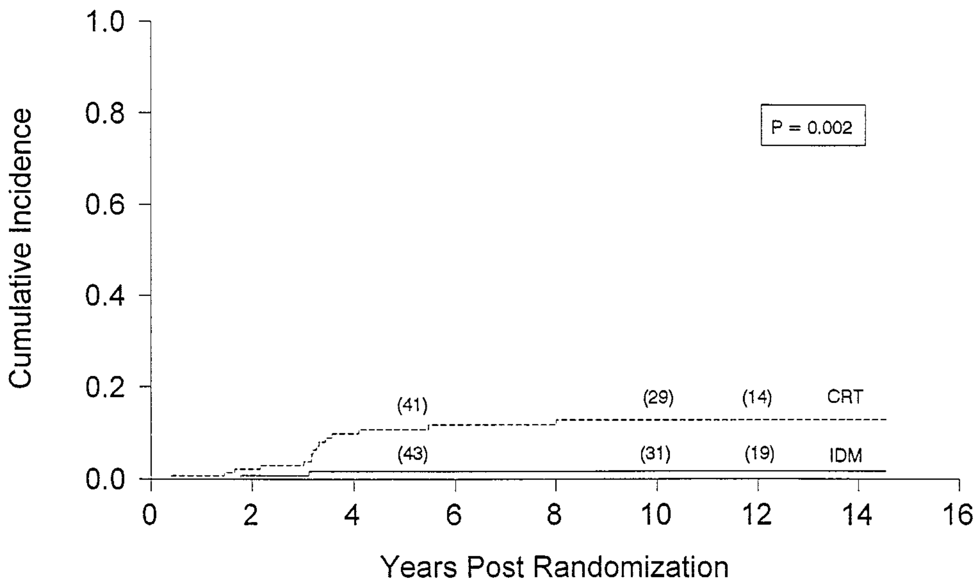

Fig. 6. Cumulative incidence functions of testicular relapse as a first event in male children with ALL treated with the IDM (N = 131) and CRT (N = 142) arms. The numbers in parentheses above the plots are the numbers of patients who remain at risk for failure at 5, 10, and 12 years. The estimates of 12-year incidence rates for the IDM and CRT arms are 2 ± 1% and 13 ± 3%, respectively.

EFS of 37 ± 3.6% is not different from the 36 ± 2.0% reported from St. Jude Children's Research Hospital from a similar era [11].

In 3,502 person-years of survival on CALGB 7611, there have been two reported second malignancies, but both occurred following salvage therapy after initial relapse. These two cancers were observed in 727 person-years of postrelapse survival. The first case, initially randomized to IDM, developed an isolated CNS relapse, and was retreated utilizing CRT; and 7 years later glioblastoma multiforme occurred. The second case initially randomized to CRT relapsed hematologically and 3 years after retrieval therapy developed acute myelocytic leukemia. In the latter case, retrieval therapy included daunorubicin, etoposide, and cyclophosphamide. Both of these patients died. The ratio of the observed incidence of new primary neoplasms to that predicted for this group of children by the SEER data is 3.71 and well within the 95% confidence interval of (0.28, 8.3). This indicates that a statistically significant excessive number of second primary neoplasms did not occur compared to the population of healthy children at large. No case of clinical cardiopathy was reported in either treatment arm of CALGB 7611.

DISCUSSION

CALGB 7611 was a randomized comparison between two treatment regimens. One was IDM given early on as

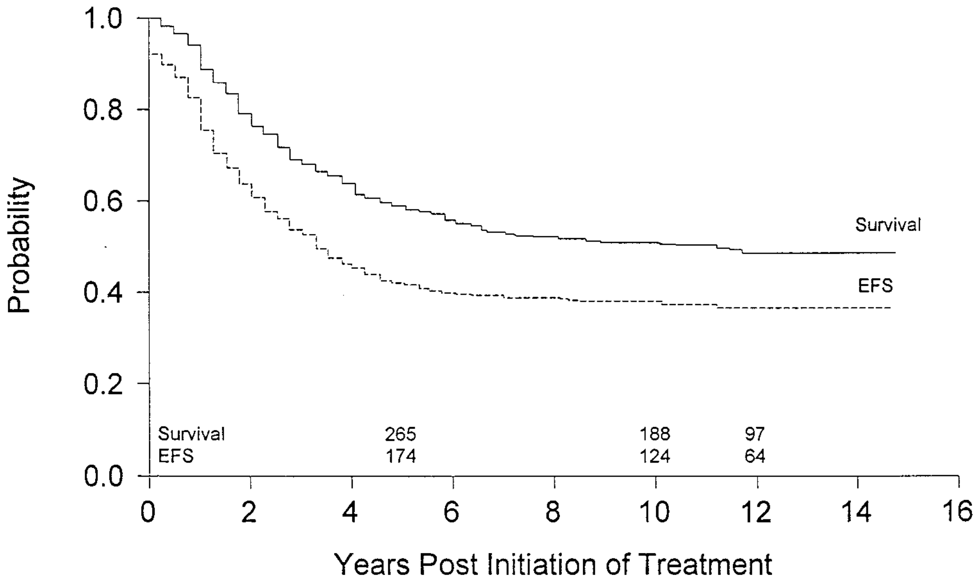

Fig. 7. Duration of EFS and survival for all eligible patients (N = 596) treated on CALGB 7611. The numbers above the time axis are the numbers of patients who remain at risk for failure at 5, 10, and 12 years. The estimate of 12-year EFS rate is 37 ± 3.6% and survival is 49 ± 3.5%.

intensification and as part of CNS therapy. The other was CRT of 2,400 cGy. Both treatment groups received six doses of IT MTX; three during induction and three with the CNS phase. The 1983 report indicated that IDM offered better protection for bone marrow and testes whereas CRT was better for CNS protection [1]. In 1991, the pattern of results in CALGB 7611 remained the same. At both analyses, overall survival and EFS were not different between the two arms.

By today's standards, the intensity of intrathecal chemotherapy utilized in the IDM arm was insufficient. Recent studies [12–17], particularly those with triple intrathecal drug therapy (methotrexate, cytosine arabinoside, and hydrocortisone) [14,15], suggest improved protection from CNS leukemia [14,15]. A study by Pullen et al. [16] demonstrated that triple intrathecal chemotherapy given over an extended time frame offered better CNS protection than IDM, but there was no difference between the two arms in overall outcome.

Since our 1983 report there have been many studies using methotrexate at intermediate or high doses [18–28] as first-line therapy or with retrieval therapy [2]. In general, results of first-line therapies are better than those reported from 7611, likely due to more intensive CNS therapy, and consequently, less CNS relapse. Poplack et al. [26], using repeated "industrial dose" methotrexate intravenously at 33.6 mg/m^2 per dose, have shown encouraging preliminary results in preventing CNS leukemia. This same dose of methotrexate (33) given as a single dose 5 days prior to more standard induction therapy has improved EFS [27]. Of particular note is the Pediatric Oncology Group (POG) study where back-to-back methotrexate and 6-MP at 1 g/m^2 of each as intensification has resulted in a greater than 90% EFS in standard-risk patients with ALL [25]. Other studies, including one from St. Jude Children's Research Hospital, have also shown the benefit of IDM in standard-risk patients in improving the overall cure rate [19,20]. Although most studies utilize methotrexate with considerable care, there appears to be little standardization of the timing or total dose of leucovorin. It has been shown that leucovorin can in fact neutralize the beneficial effects of methotrexate [29–31]. One study showing no disease-free survival beneift from IDM [32] employed multiple doses of leucovorin. CALGB 7611 employed only a single dose of leucovorin at 12 mm/m^2 following 48 hours of methotrexate exposure. Rapid body clearance of methotrexate has also been shown to decrease efficacy [33]. Recent studies have employed methotrexate doses greater than 500 mg/m^2.

Following elective cessation at therapy of 3 years, a subsequent 30 ± 5% failure rate was noted; this is similar to that reported by Pui et al. [34] from St. Jude Children's Research Hospital where they noted a 22–24% relapse rate.

Of interest was the retrieval rate following relapse. These patients have now been followed for more than 5 years of CCR after reinduction and thus this appears to be authentic salvage. For patients who relapsed while on therapy or within 6 months after the cessation of therapy, the 10-year retrieval rate was 20 ± 5%. In patients who relapsed after 6 months off-therapy, the 5-year salvage rate was 49 ± 10%. These figures are somewhat higher than other reports of salvage following late relapse [35–38]. Since the recent analysis did not determine what type of salvage therapy was employed, it is not clear how many of these patients had bone marrow transplants. This high salvage rate may also reflect that by today's stan-

dards many of these patients initially received relatively nonaggressive therapy.

CALGB 7611 did not use anthracyclines and no instance of clinical cardiopathy was reported, although these patients did not undergo cardiac assessment. Anthracyclines have been observed to result in unexpected late cardiopathies, even at cumulative doses of less than 300 mg/m^2 [39,40]. At a median follow-up of 6.4 years following completion of therapy, there were echocardiographic abnormalities reported in 65% of survivors of childhood ALL when doxorubicin was incorporated into the leukemia therapy [39]. Although only approximately 10% of the survivors had evidence of overt cardiopathy (congestive failure), these individuals are young adults and it is feasible that this figure will rise considerably over the ensuing years. In fact, it has been suggested that survivors of childhood cancers now represent one of the largest new groups at risk for premature cardiovascular disease [41].

Sandoval et al. [42] have reported that the combination of radiation with alkylators and topoisomerase II inhibitors may cause secondary acute myelocytic leukemia [42]. Based upon the review of four series, Ratain and Rowley [43] suggest that the combination of anthracyclines and other intercalating agents (topoisomerase II inhibitors), when combined iwth alkylating agents, appears to be leukemogenic. Data from Pedersen-Bjergaard et al. [44] support this concept. CALGB 7611 did not utilize these drug combinations, nor did it combine CRT with alkylators or with topoisomerase II inhibitors.

Second neoplasms have been reported following treatment of ALL, particularly in those patients receiving CRT as CNS prophylaxis [45,46]. The epipodophyllotoxins have recently been implicated as playing a role in secondary acute myelocytic leukemia [47,48]. In CALGB 7611, second primaries in patients remaining in CCR were not seen on either arm of therapy. The two cases of second cancers observed following retrieval therapy received CRT and known carcinogenic drugs. Even including these two cases, the number of second primaries is not significantly different from that predicted by the SEER data in a comparable group of normal children in the population at large. The reason for the low rate for second primaries may be related to the fact that with the exception of CRT, the treatment regimens did not contain known carcinogens [2].

CONCLUSIONS

Given the increasing cure rate, the quality of life in survivors of ALL has become an important issue. Patients treated on CALGB 7611 were evaluated with neuropsychological tests. Those patients who received CRT attained significantly lower full-scale IQs and performed more poorly on the Wide Range Achievement Test [49]. Very recently, 110 survivors of CALGB 7611 were again evaluated, now as young adults. Survivors who received CRT and IT MTX were found to have significantly worse adaptation. This was mainly due to greater psychological distress, worse body image, and poor academic achievement [50]. The results of these evaluations will be described in detail in a subsequent paper.

By the year 2010, 1 in 250 adults between the ages of 20 and 45 in the United States will be a survivor of childhood cancer [51]. Careful risk benefit analyses based on extensive long-term follow-up are necessary when one is considering the design of new studies in childhood ALL using carcinogenic agents and other agents with potentially late debilitating toxicities. These risks may be justified if survival rates are significantly greater than those achieved with CALGB 7611 therapy which has proved to be risk free for second cancers and cardiac dysfunction.

ACKNOWLEDGMENTS

We thank Dr. Robert J. Gray for providing the Fortran programs used to estimate and test the cumulative incidence functions. Supported in part by a grant from The Martel Foundation, NCI Grant CA 21765 and The American Lebanese Syrian Associated Charities.

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